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Catharine R. Gale, G. David Batty, David P. J. Osborn, Per Tynelius and Finn Rasmussen

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Mental Disorders Across the Adult Life Course and Future Coronary Heart Disease

Evidence for General Susceptibility

Catharine R. Gale, PhD; G. David Batty, PhD; David P. J. Osborn, PhD; Per Tynelius, MSc; Finn Rasmussen, PhD

Background—Depression, anxiety, and psychotic disorders have been associated with an increased risk of coronary heart disease (CHD). It is unclear whether this association between mental health and CHD is present across a wider range of mental disorders.

Methods and Results—Participants were 1 107 524 Swedish men conscripted at a mean age of 18.3 years. Mental disorders were assessed by psychiatric interview on conscription, and data on hospital admissions for mental disorder and CHD were obtained from national registers during 22.6 years of follow-up. An increased risk of incident CHD was evident across a range of mental disorders whether diagnosed at conscription or on later hospital admission. Age-adjusted hazard ratios (95% confidence intervals) according to diagnoses at conscription ranged from 1.30 (1.05–1.60) (depressive disorders) to 1.92 (1.60–2.31) (alcohol-related disorders). The equivalent figures according to diagnoses during hospital admission ranged from 1.49 (1.24–1.80) (schizophrenia) to 2.82 (2.53–3.13) (other substance use disorders). Associations were little changed by adjustment for parental socioeconomic status, or body mass index, diabetes mellitus, and blood pressure measured at conscription, but they were partially attenuated by the adjustment for smoking, alcohol intake, and intelligence measured at conscription, and for education and own socioeconomic position.

Conclusions—Increased risk of incident CHD is present across a range of mental disorders and is observable when the disorders are diagnosed at a young age. **(*Circulation*. 2014;129:186-193.)**

Key Words: cohort studies ■ epidemiology ■ heart diseases ■ men ■ mental disorders.

There is considerable evidence that some forms of mental disorders are associated with an increased risk of coronary heart disease (CHD). Systematic reviews demonstrate that depression is associated prospectively with an increased risk of CHD.[1–4] The role of anxiety in determining CHD risk has been less studied, but anxiety has also been linked with incident CHD.[5,6] Schizophrenia and other psychoses have been associated with excess CHD mortality.[7–9] These findings suggest that the link between mental disorders and CHD risk may not be confined to a few disorders or to those whose disorder is severe.

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The reasons why some forms of mental disorder are linked with an increased risk of CHD are not fully understood. People with psychotic illnesses tend to have a high prevalence of risk factors such as poor health behaviors, obesity, and diabetes mellitus.[8,10,11] Hypertension may occur more frequently in such individuals.[10] Psychotropic medications—often prescribed for long periods—have been associated with weight gain, dyslipidemia, and impaired glucose homeostasis.[12–14] Severe mental illness is associated with negative consequences such as lack of social support and socioeconomic disadvantage.[15,16] However, the lack of studies with detailed covariate data means that the extent to which individual risk factors explain associations between severe mental disorder and CHD risk remains uncertain. Most studies of the relation between depression or anxiety and CHD risk had data on some potential confounding or mediating factors,[1–3,5] but vary in the covariables they controlled for, so the role of several major risk factors in determining CHD risk in people with these or other nonpsychotic mental disorders remains unclear.

In this study, we used data on >1 million Swedish men who underwent psychiatric and medical assessment during military conscription examinations in early adulthood and were followed up for hospital admission for psychiatric

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.002065/-/DC1.

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disorder and for CHD. Our first objective was to investigate whether the risks of incident CHD associated with a range of mental disorders diagnosed in youth are similar to those associated with subsequent hospital admission for these disorders. If mental disorder in men so young is associated with an increased risk of CHD, it would help rule out the possibility of reverse causation whereby subclinical vascular disease might cause mental distress.[17] Our second objective was to examine the extent to which risk factors at conscription (blood pressure, body mass index, diabetes mellitus, smoking, alcohol intake, and intelligence), together with socioeconomic circumstances in childhood or adult life, explained any associations.

Methods

Study Participants

The record linkage methods used to generate the cohort have been reported previously.[18] The cohort comprised all nonadopted men born in Sweden from 1950 to 1976 for whom both biological parents could be identified in the Multi-Generation Register. Using personal identification numbers, we linked the Multi-Generation Register with the Military Service Conscription Register, Population and Housing Censuses records, Education Register, the Cause of Death Register, and the National Hospital Discharge Register. This produced 1 346 545 successful matches. The Regional Ethics Committee, Stockholm, approved the study.

Conscription Examination

The examination involves a standard medical assessment of physical and mental health, and intelligence. During the years covered by this study, the law required this examination; only men of foreign citizenship or with severe disability were excused. This data set covers examinations from September 15, 1969 to December 31, 1994. Average age was 18.3 years.

Blood pressure, height, and weight were measured with the use of standard protocols. Body mass index (BMI, kg/m^2) was calculated. Diagnoses of diabetes mellitus were recorded during the medical examination. Men underwent a structured interview by a psychologist. Those who presented psychiatric symptoms were assessed by a psychiatrist. Diagnoses were made according to the Swedish version of the *International Classification of Diseases* (ICD), eighth and ninth revisions.

Socioeconomic status (SES) in early life was based on the highest occupation of either parent from the 1960/1970 Censuses. The 1990 Census records were used to ascertain own SES. SES was classified as nonmanual (high/intermediate), nonmanual (low), skilled, unskilled, and other. These census records and the Educational Register (1990 onward) were used to ascertain highest educational level, classified as <9 years of primary school, 9 to 10 years of primary school, full secondary school, or higher education. Data on own SES and education were available for a subset of the cohort. Intelligence was measured by 4 subtests representing verbal, logical, spatial, and technical abilities from which a total score (IQ) was calculated.[19]

For participants conscripted from 1969 to 1970 only, information was collected on smoking (>20, 11–20, 6–10, 1–5 cigarettes/d; nonsmoker) and alcohol consumption. Risky use of alcohol was defined as the presence of at least one of the following: (1) consumed ≥250 g of 100% alcohol per week, (2) ever consumed alcohol during a hangover, (3) ever apprehended for drunkenness, and (4) had often been drunk (response options in the questionnaire were often, rather often, sometimes, and never).[20]

Hospital Admissions for Psychiatric Disorders

The Swedish National Hospital Discharge Register—founded in 1964—has data on inpatient psychiatric care; coverage has been virtually complete since 1973.[21] Admissions were coded according to the Swedish version of the ICD, eighth, ninth, or tenth revisions. We extracted data on admissions from 1968 to December 31, 2004.

As in a previous study,[22] we grouped diagnoses (primary and secondary) from the conscription examinations and hospital admissions into categories by using the ICD codes shown Table I in the online-only Data Supplement: schizophrenia, other nonaffective psychotic disorders (excluding alcohol or drug psychoses), bipolar disorders, depressive disorders, neurotic and adjustment disorders, personality disorders, alcohol-related disorders (including alcoholic psychoses), and other substance use disorders (including drug psychoses).

Coronary Heart Disease

Data on fatal or nonfatal CHD events during the follow-up period were obtained from the Cause of Death Register and the National Hospital Discharge Register. Cases were identified according to the Swedish version of the ICD, eighth, ninth, or tenth revisions, by using codes 410 to 414 from ICD, eighth and ninth revisions, and codes I20 to I25 from the ICD, tenth revision.

Analytic Sample

Of 1 346 545 men with matched records, 1 107 646 had complete data from the conscription examination and parental SES. We excluded 72 men diagnosed with CHD at conscription and used the remaining 1 107 524 to examine the relation between mental disorders at conscription and incident CHD. To examine the relation between diagnoses of mental disorders on admission to hospital after conscription and incident CHD, we used a subsample of 1 099 304 men who had no history of psychiatric hospitalization.

Statistical Methods

We used Cox proportional hazards models to examine the risk of CHD according to diagnoses of mental disorder at conscription. Survival time in days was calculated from the date of conscription to date of death, hospitalization with CHD, emigration, or December 31, 2004, whichever occurred first. In total, 90.1% of the participants were followed up to December 31, 2004. We adjusted for age at conscription, conscription testing center, and year of testing; then, in addition, for parental SES, BMI, diabetes mellitus, diastolic blood pressure, and IQ. Because some men were too young to have an occupation at the time data on own SES were collected in the 1990 Census, we performed further adjustment for own SES and education in the subset of men who were ≥25 years of age in 1990. We used diastolic blood pressure because it predicts cardiovascular mortality more strongly than systolic blood pressure in this cohort.[23] In the subset with data on smoking and alcohol intake, we examined the effect of adjustment for these factors. The analyses of mental disorder on hospital admission as a risk factor for CHD were performed identically, the only difference being the modeling of the exposure as time varying. We investigated the presence of secular trends by examining whether hazard ratios changed after accounting for birth year in stratified models and if associations varied according to year of birth.

We estimated the impact on the hazard ratio (HR) of adjusting for individual covariates using the formula[24]: $([HR_{\text{adjusted for age}} - 1] - [HR_{\text{adjusted for age and covariate}} - 1]/[HR_{\text{adjusted for age}} - 1]) \times 100$.

Results

Mental Disorders at Conscription

At conscription, 62 868 (5.7%) men were diagnosed with mental disorders. Of those, 72% had 1 diagnosis, 18% had 2 diagnoses, and 10% had 3 to 5 diagnoses. During the mean follow-up period of 22.6 years, there were 12 357 cases of CHD; 1440 were fatal.

Table 1 shows HRs (95% confidence intervals) for incident CHD according to mental disorder at conscription. (There were too few CHD events among the small number diagnosed with bipolar disorder or schizophrenia for separate analysis,

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Table 1. Hazard Ratios (95% CI) for Coronary Heart Disease Events According to Diagnosis of Mental Disorders at Conscription (n=1 107 524)

Diagnostic Category	Diagnoses, n (%)	Hazard Ratio (95% CI)		
		Adjusted for Age	Adjusted for All Covariables, Except Own SES and Education*	Adjusted for All Covariables, Including Own SES and Education†
Other nonaffective psychoses/ schizophrenia/bipolar disorder	12 595 (1.14)	1.91 (1.70–2.15)	1.16 (1.03–1.31)	1.16 (1.02–1.31)
Depressive disorders	9402 (0.85)	1.30 (1.05–1.60)	1.21 (0.98–1.50)	1.22 (0.98–1.53)
Neurotic/adjustment disorders	48 039 (4.34)	1.52 (1.43–1.62)	1.29 (1.21–1.37)	1.26 (1.18–1.34)
Personality disorders	9185 (0.83)	1.46 (1.31–1.62)	1.29 (1.16–1.43)	1.24 (1.12–1.38)
Alcohol-related disorders	2688 (0.24)	1.92 (1.60–2.31)	1.46 (1.22–1.76)	1.37 (1.12–1.64)
Other substance use disorders	9547 (0.86)	1.35 (1.12–1.63)	1.25 (1.04–1.51)	1.22 (1.01–1.48)

All adjustments include conscription testing center and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. CI indicates confidence interval; and SES, socioeconomic status.

*Further adjusted for parental SES, body mass index, diastolic blood pressure, diabetes mellitus, and intelligence.

†Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=666 190).

so these diagnoses have been grouped with other nonaffective disorders.) In analyses adjusting for age at conscription, conscription testing center, and year of testing, men diagnosed with a mental disorder had a risk of incident CHD that was between 1.30 and 1.92 times higher than those who had not been so diagnosed. After further adjustment for parental SES, BMI, diabetes mellitus, diastolic blood pressure, and IQ, the associations were attenuated by 29% to 82%. Further adjustment for education and own SES in a subset aged ≥25 years at SES data collection attenuated the association between alcohol-related disorders and CHD by an additional 20%, but this adjustment had a less attenuating effect on the other associations. Adjustment for BMI attenuated the association with diagnoses of schizophrenia, other nonaffective psychoses, or bipolar disorder and risk of CHD by 66% (Table II in the online-only Data Supplement). After adjustment for all covariables, the association between depressive disorders and risk of CHD was no longer significant, but diagnoses of all other mental disorders remained predictors of CHD risk. When all diagnoses of mental disorder were considered together, age-adjusted risk of CHD associated with having any mental disorder was 1.53 (1.46–1.62); after further adjustment for all covariates with the exception of own SES and education or all covariates including own SES and education, the HRs were 1.31 (1.25–1.39) and 1.28 (1.21–1.35), respectively. We examined whether associations between mental disorders and the risk of CHD varied significantly according to the covariables, but we found no evidence of interactions.

To investigate whether psychiatric comorbidity at conscription or a subsequent history of psychiatric hospitalization inflated the magnitude of these associations, we repeated our analyses, excluding these groups in turn. Excluding cases with a comorbid mental diagnosis at conscription weakened associations, particularly in the case of those diagnosed with schizophrenia, bipolar disorder, or other nonaffective disorders, and some associations became nonsignificant after full adjustment, but the most commonly diagnosed disorders remained predictors of CHD (Table III in the online-only Data Supplement). The exclusion of cases with a subsequent history of psychiatric hospitalization had a more marked attenuating effect, suggesting that some of the excess risk of CHD associated with diagnosis of a mental disorder at conscription may be concentrated in those with severer forms of disorder, although it is noteworthy that the most common diagnosis, neuroticism/adjustment disorders, remained a significant predictor even with this exclusion (Table IV in the online-only Data Supplement).

Some 8220 men (0.7%) had a history of psychiatric hospitalization before conscription. Only 19% of these were diagnosed with a mental disorder at conscription, perhaps because they had recovered or did not report symptoms. Men with a history of psychiatric hospitalization who were not diagnosed with a mental disorder at conscription had an increased risk of CHD; in comparison with men who had no such history, their fully adjusted risk of CHD was 1.42 (1.01–2.03). Underdiagnosis of mental disorder at conscription might mean our results do not accurately reflect the effect of such diagnoses on CHD risk. We repeated our analyses excluding men admitted to a psychiatric hospital before conscription. Effect sizes were little changed (Table V in the online-only Data Supplement).

Table 2 shows the extent to which smoking and alcohol intake at conscription accounted for the link between mental disorder and risk of CHD in the subset with data on these factors. There were 1504 incident CHD events in this subset. Because of the small number of events in some diagnostic groups, we grouped all diagnoses together. The age-adjusted HR of CHD associated with the diagnosis of any mental disorder in this subset was 1.21 (1.03–1.42), weaker than the equivalent HR found in the cohort as a whole, 1.53 (1.46–1.62). Additional adjustment for smoking and risky alcohol intake at conscription attenuated this association by 86% such that it was no longer statistically significant. It was weakened further by full adjustment.

Mental Disorders on Hospital Admission

These analyses are based on 1 099 304 men with no previous history of psychiatric hospitalization. In total, 60 328 men (5.5%) had at least 1 admission for a mental disorder during follow-up. Mean (standard deviation) age of first admission was 32.0 (9.34) years. Of those admitted, 62% were diagnosed with 1 disorder only, 23% were diagnosed with 2 disorders,

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Table 2. Hazard Ratios (95% CI) for Coronary Heart Disease Events According to Diagnosis of Any Mental Disorder at Conscription: Men Conscripted in 1969 to 1970 Only (n=34 195)

		Hazard Ratios (95% CI)			
Diagnostic Category	Diagnoses, n (%)	Adjusted for Age	Adjusted for Age, Smoking Habits, and Risky Alcohol Intake	Adjusted for All Covariables Except Education and Own SES*	Adjusted for All Variables Including Education and Own SES†
Any mental disorder	3390 (9.91)	1.21 (1.03–1.42)	1.03 (0.88–1.22)	0.97 (0.83–1.14)	0.96 (0.82–1.13)

All adjustments include conscription testing center and year of examination. CI indicates confidence interval; and SES, socioeconomic status.
*Further adjusted for parental SES, body mass index, diabetes mellitus, diastolic blood pressure, and intelligence.
†Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=33 588)

9% were diagnosed with 3 disorders, and 6% were diagnosed with 4 to 8 disorders. Table 3 shows HRs for incident CHD according to diagnoses received during hospital admission. In contrast to the conscription examination where neurotic/adjustment disorders were the most common diagnoses, alcohol-related disorders were the most common diagnoses on hospital admission. In analyses adjusting for age at conscription, conscription testing center, and year of testing, men who were admitted with a diagnosis of schizophrenia, other nonaffective psychotic disorders, bipolar disorders, depressive disorders, neurotic and adjustment disorders, personality disorders, alcohol-related disorders, or other substance use disorders had a risk of incident CHD that was between 1.49 and 2.82 times higher than those who had not been so diagnosed. After further adjustment for parental SES, BMI, diabetes mellitus, diastolic blood pressure, and IQ, the associations were attenuated by 10% to 24%. Further adjustment for education and own SES in a subset aged ≥25 years at SES data collection attenuated the age-adjusted associations by 19% to 53%. The strongest attenuating effects were caused by the adjustment for intelligence at conscription or own SES and education (Table VI in the online-only Data Supplement). When all diagnoses of mental disorders were considered together, the age-adjusted risk of CHD associated with having any mental disorder was 2.34 (2.22–2.47); after further adjustment for all covariates, with the exception of own SES and education, or all covariates including own SES and education, the HRs were 2.13 (2.02–2.25) and 2.04 (1.92–2.15), respectively. We examined whether associations between mental disorders and risk of CHD varied significantly according to the covariables but found no evidence of interactions.

To explore whether the increased risk associated with hospital admission for mental disorder was concentrated among men with comorbidity, we repeated our analyses excluding these men. Estimates were lower and associations with less common diagnoses were markedly weakened after full adjustment, but, even when diagnosed in a pure form, most disorders were predictive of CHD (Table VII in the online-only Data Supplement).

The correlation between diagnosis of any mental disorder at conscription and on hospital admission was 0.12 ($P<0.0001$). Only 17% of those admitted to a psychiatric hospital had been diagnosed with a mental disorder at conscription. The risk of CHD associated with diagnosis of any mental disorder on hospital admission in this group of men was very similar to that observed in those with no previous diagnosis at conscription: age-adjusted HR 2.22 (2.01–2.46) versus 2.27 (2.13–2.41).

Table 4 shows the extent to which smoking and risky alcohol intake at conscription accounted for the link between any mental disorder diagnosed on hospital admission and CHD in the subset with these data. Men in this subset who were diagnosed with a mental disorder had a 2-fold risk of CHD. Adjustment for smoking habits or risky alcohol intake at conscription attenuated this association by 31%. Further adjustment for other covariables slightly strengthened this association.

Table 3. Hazard Ratios (95% CI) for Coronary Heart Disease Events According to Diagnosis of Mental Disorders on Hospital Admission After Conscription (n=1 099 304)

		Hazard Ratios (95% CI)		
Diagnostic Category	Diagnoses, n (%)	Adjusted for Age	Adjusted for All Covariables Except Education and Own SES*	Adjusted for All Covariables Including Education and Own SES†
Schizophrenia	5961 (0.54)	1.49 (1.24–1.80)	1.37 (1.13–1.64)	1.23 (1.02–1.49)
Other nonaffective psychoses	6446 (0.59)	1.82 (1.52–2.18)	1.67 (1.39–2.00)	1.58 (1.31–1.90)
Bipolar disorders	2566 (0.23)	1.62 (1.21–2.18)	1.56 (1.16–2.10)	1.49 (1.09–2.02)
Depressive disorders	14 519 (1.32)	2.09 (1.87–2.33)	1.94 (1.73–2.16)	1.87 (1.68–2.10)
Neurotic/adjustment disorders	18 330 (1.67)	2.45 (2.24–2.69)	2.25 (2.05–2.47)	2.17 (1.98–2.38)
Personality disorders	6917 (0.63)	2.01 (1.73–2.33)	1.79 (1.54–2.08)	1.63 (1.40–1.91)
Alcohol-related disorders	28 391 (2.58)	2.62 (2.44–2.81)	2.31 (2.16–2.48)	2.16 (2.01–2.32)
Other substance use disorders	13 226 (1.20)	2.82 (2.53–3.13)	2.54 (2.29–2.83)	2.30 (2.06–2.57)

All adjustments include conscription testing center and year of examination. CI indicates confidence interval; and SES, socioeconomic status.
*Further adjusted for parental SES, body mass index, diagnosed diabetes mellitus, diastolic blood pressure, and intelligence, all measured at conscription.
†Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=662 983).

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Table 4. Hazard Ratios (95% CI) for Coronary Heart Disease Events According to Diagnosis of Any Mental Disorder on Hospital Admission After Conscription: Men Conscripted in 1969 to 1970 Only (n=34 290)

		Hazard Ratios (95% CI)			
Diagnostic Category	Diagnoses, n (%)	Adjusted for Age	Adjusted for Age, Smoking Habits, and Risky Alcohol Intake	Adjusted for All Covariables Except Education and Own SES*	Adjusted for All Variables Including Education and Own SES†
Any mental disorder	3161 (9.2)	2.03 (1.74–2.36)	1.72 (1.47–2.01)	1.83 (1.57–2.14)	1.76 (1.50–2.07)

All adjustments include conscription testing center and year of examination. CI indicates confidence interval; and SES, socioeconomic status.
*Further adjusted for parental SES, body mass index, diagnosed diabetes mellitus, diastolic blood pressure, and intelligence, all measured at conscription.
†Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=33 583)

Secular Trends

In analyses controlling for birth year by the use of stratified Cox models, estimates of overall CHD risk associated with diagnosis of any mental disorder, either on conscription or on hospital admission, were almost identical to those obtained without control for birth year. However, the association between mental disorder and risk of CHD differed according to birth year (*P* for interaction terms=0.03 in the case of mental disorder at conscription and <0.0001 in the case of mental disorder on hospital admission). In analyses by birth year group (Table VIII in the online-only Data Supplement), the proportion of men diagnosed with a mental disorder at conscription or on hospital admission was lower in later born men. The risk of CHD associated with such a diagnosis at conscription was slightly higher in later born men, but there was no clear evidence of a trend across birth year groups after adjustment for covariables. The risk of CHD associated with such a diagnosis on hospital admission rose with a later year of birth and persisted after adjustment.

Discussion

We examined the risk of incident CHD in 2 groups with mental disorders, one comprising young men diagnosed during a psychiatric examination at conscription, and one made up of men whose illness required hospital admission during follow-up. Age-adjusted HRs (95% confidence interval) according to diagnoses at conscription ranged from 1.30 (1.05–1.60) to 1.92 (1.60– 2.31). The equivalent figures according to diagnoses during hospital admission ranged from 1.49 (1.24–1.80) to 2.82 (2.53–3.13). Parental SES played little part in these associations. In general, adjustment for BMI, blood pressure, or history of diabetes mellitus at conscription had modest or no attenuating effects, but we were unable to take account of how levels of these risk factors might have changed after conscription because no such data were available. Intelligence, education, and own SES accounted for part of the associations, but virtually all associations persisted after adjustment for these factors. Smoking and risky alcohol intake, measured at conscription only, explained, to a large degree, the link between mental disorder at that time and subsequent CHD, and partially accounted for some associations between later hospital admission for mental disorders and CHD risk. The risk of CHD associated with psychiatric hospital admission was greater in later born men than those born earlier.

Previous longitudinal studies of the link between mental disorders and the risk of CHD have primarily been based either on individuals diagnosed with psychotic disorders,[7–9]or on those with depression[1–3] or anxiety[5,6] Here, we examined the impact on CHD risk of a wide range of mental disorders, including personality disorders and substance use disorders. The highest risks of CHD tended to be in those whose mental disorder required hospital admission, and this increased risk was present across the range of diagnostic groups. Risk of CHD was also increased, to a lesser extent, in men diagnosed with the same range of disorders in early adulthood. These findings show that the link between mental illness and subsequent CHD is not confined to a few specific mental disorders or to those with more chronic or perhaps more severe illness. They also add to the very limited evidence on the relation between early-onset mental disorders and CHD risk. In a small subset of men from the present cohort born in 1969 to 1970, diagnoses of anxiety, but not depression, in early adulthood were associated with increased risk of CHD.[25] In this much larger sample, we show that the onset of the range of mental disorders in early adulthood is associated with an increased likelihood of developing CHD.

Our finding that the risk of CHD associated with hospitalization for mental disorders tended to be higher than that associated with diagnosis of mental disorders at conscription suggests that the severity of mental illness may play some part. Consistent with this finding, education and own SES appeared to have a stronger mediating role in the association between mental disorders and CHD risk among men diagnosed on hospital admission than among those diagnosed at conscription. Deprivation and poor living conditions are risk factors for physical illness and occur more commonly in people with severe mental disorder. Mental illness may affect educational attainment and achieved SES, but lower SES directly, and indirectly through adverse economic circumstances, also increases the risk of mental disorders.[26]

Some of the highest HRs for CHD were observed in the most commonly diagnosed mental conditions that might be perceived as less severe, namely neurotic or adjustment disorders. This pattern was present in regard to diagnoses both at conscription and on hospital admission. These observations demonstrate that a broad spectrum of mental disorders is associated with later risk of CHD. Given that neurotic or adjustment disorders occur far more frequently in the general population than psychotic disorders, the population-attributable risk for these conditions with respect to CHD will be greater.

Lower intelligence in youth has been linked with an increased risk of mental disorders[19,27] and CHD.[28] Here, intelligence accounted for between 15% and 43% of the

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associations between mental disorders and risk of CHD. It may also have an indirect role via its influence on educational attainment and achieved SES[29]or behavioral or physiological risk factors.[30,31]

Other possible explanations for the associations between mental disorder and CHD are lifestyle and other modifiable risk factors, such as obesity, diabetes mellitus, dyslipidemia, and hypertension.[16,32,33] Smoking and alcohol intake at conscription explained a large part of the association between any mental disorder at that time and later CHD, but far less of the association between hospital admission for mental disorder and CHD, perhaps because they provide only a partial reflection of such behaviors at hospital admission. We had no data on these risk factors after conscription. The extent to which smoking mediates associations between mental disorder and cardiovascular disease risk in previous studies varies greatly.[7,16] Low levels of physical activity and poorer diet may be more common in people with severe forms of mental illness,[16,32,34] but we lacked data to examine their role. Prospective evidence that BMI, blood pressure, or diabetes mellitus are linked with mental disorder is inconsistent.[8,10,16,32] Here, we found little indication that these factors as assessed at conscription played a part in the associations.

Other potentially important explanations that we were unable to examine are access to physical health care and psychotropic medication. People with more severe mental disorders tend to experience poorer assessment and care of physical illness.[12–14] In a population-based study, such individuals were less likely to undergo invasive cardiac procedures after admission with CHD, suggesting that this undertreatment contributed to their excess mortality.[35]Antipsychotic, mood-stabilizing, and antidepressant medications may all affect CHD risk through their influence on cardiometabolic risk factors.[12,36] However, the direction of any association between psychotropic medication and cardiovascular risk is debated. Recent evidence suggests that people who receive pharmacological treatment for mental illness may have better cardiovascular outcomes. This has been observed in depressed people with diabetes mellitus who are treated with antidepressants,[37]and in people with severe mental illness who receive longer-term treatment with antipsychotics.[38,39]

The psychological distress experienced by those with mental disorders may have direct physiological effects that adversely influence the risk of CHD.[40] High levels of distress have been associated with elevated inflammatory markers,[41]possibly because of dysregulation of the hypothalamic-pituitary-adrenal axis, and these may accelerate the processes of atherosclerosis, coagulation, and thrombus formation.[42,43]

A propensity to psychological distress, known as type D (distressed) personality, may increase the susceptibility to mental disorders[44] and have an adverse effect on prognosis in cardiovascular disease.[45] Type D personality has been linked with the risk of CHD in a cross-sectional study,[46] but there is no evidence as to whether it is a risk factor for incident CHD. We were not able to explore its potential explanatory role here.

Among the strengths of this study are its size and data on diagnoses made during the conscription examination that enabled us to examine associations between clinical diagnoses of a range of mental disorders and risk of CHD in a nonpsychiatric sample. The availability of information on intelligence, BMI, diabetes mellitus, blood pressure, smoking habits, and alcohol intake at conscription allowed us to explore the extent to which these explained associations between mental disorder and risk of CHD. The youthfulness of our sample at conscription makes it highly unlikely that the associations between mental disorder at that time and later CHD are attributable to reverse causation, in other words, that subclinical manifestations of vascular disease might cause mental distress.[17]

Our study also has some weaknesses. It is based on men. The extent to which these findings apply to women is uncertain. Some studies have found that psychoses are more strongly associated with cardiovascular mortality in men than women, but this is not a consistent finding.[7] Existing evidence suggests that the relation between anxiety or depression and subsequent risk of CHD differs little by sex.[2,3,5] Although we had data on some risk factors at conscription, we had no information on other potentially important mediating factors such as exercise or diet,[33] or on risk factors after conscription. Because some men were first admitted up to 22 years after conscription, the measurements made at conscription may not reflect these characteristics at hospital admission. In 3% of cases, CHD occurred before the measurement of own SES and education, so for these individuals these variables may not accurately reflect the levels of these factors before illness developed. We had no data on psychiatric diagnoses made in primary care or as outpatients during follow-up or on use of psychotropic medication, so we were unable to examine how these factors affected CHD risk. The extent of mental disorder at or before conscription may have been underestimated because referral for psychiatric assessment depended on whether men reported symptoms suggestive of mental health problems during the psychological examination, and data on psychiatric hospitalization were incomplete prior to 1973; furthermore, men with severely disabling illness were excused from conscription. On the other hand, malingering may have led some men to report symptoms falsely in the hope of being excused from military service. Our findings may therefore underestimate the true strength of the association between mental disorders in the general population of young men and the risk of CHD. Mental disorders were diagnosed less frequently at conscription in later born men than in those born earlier. Owing to military secrecy, no information is available on whether this is attributable to changes in how psychiatric disorders were assessed at the conscription examination. Whether the higher prevalence of mental disorder at conscription in earlier born men reflects the inclusion of less severe cases is unclear, but the relative weakness of the association between conscription mental disorder and CHD risk in the subset with smoking and alcohol data, men all born in 1951, suggests this might be an explanation. Finally, inpatient psychiatric care in Sweden, as elsewhere, has become increasingly less common.[47] The men who were identified as having mental disorders on the basis of hospital admission are therefore likely to be those with more severe illness. This may explain why the risk of CHD associated with hospital admission for mental disorder appeared higher in later born men, although it is important to note that these men were followed up for a shorter period than those

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born earlier, so estimates of risk are based on fewer events and may be less reliable.

Conclusions

Our findings demonstrate that the increased risk of incident CHD previously associated with some forms of mental illness is present across the range of mental disorders. If this huge burden of premature illness and death attributable to CHD is to be reduced, the physical health care of people with mental illness needs to be a greater priority.

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Disclosures

None.

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CLINICAL PERSPECTIVE

There is evidence from longitudinal studies that people with schizophrenia and other psychotic disorders have an increased risk of developing coronary heart disease (CHD). Depression and anxiety have also been linked with an increased risk of CHD. Whether mental disorder in general—even in milder forms—makes people more susceptible to CHD and what factors explain this increased risk has been unclear. In this longitudinal study of >1 million men, we found that a wide range of mental disorders—schizophrenia, other nonaffective psychotic disorders, bipolar disorders, depressive disorders, personality disorders, alcohol-related and other substance use disorders, and the most common forms of mental illness, neurotic and adjustment disorders—were associated with an increased risk of CHD. This increased risk was evident both in young men diagnosed with mental disorders at ≈18 years of age during a psychiatric examination on conscription and in older men diagnosed on later psychiatric hospital admission. Smoking and risky alcohol intake at 18 years of age explained to a large degree the link between mental disorder at that time and subsequent CHD, but virtually all associations persisted after the adjustment for early-life socioeconomic status, body mass index, diabetes mellitus, blood pressure and intelligence measured at conscription, and education and later-life socioeconomic position. Our findings suggest that mental disorders pose a huge public health burden in terms of premature illness and death attributable to CHD. The physical health care of people with mental disorders needs to be a priority for clinicians if this burden is to be reduced.

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Diagnostic categories and codes according to the 8th, 9th& 10th revision of the ICD

Diagnostic category	ICD-8	ICD-9	ICD-10
Schizophrenia	295	295	F20-21, F25
Other non-affective psychoses	297.0-9, 298.2-3, 298.9	297, 298.2-4, 298.8-9	F22-24, F28-29
Bipolar disorders	296.1, 296.3, 298.1	296.0, 296.2-5, 298.1	F30-31
Depressive disorders	296.0, 296.2, 298.0, 300.4	296.1, 298.0, 300.4, 311	F32-34, F38-39
Neurotic/ adjustment disorders	300.0-3, 300.5-9, 305, 307	300.0-3, 300.5-9, 306, 308-9	F40-48
Personality disorders	301	301	F60-69
Alcohol-related disorders	291, 303	291, 303, 305.0	F10
Other substance use disorders	294.3, 304	292, 304, 305.1-8;	F11-F19

Abbreviations: ICD, International Classification of Diseases

Supplemental table 2. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders on conscription, separately and fully adjusted for the covariables (n=1,107,524)

		Hazard ratios (95% confidence intervals)							
		Adjustments							
Diagnostic category	**No (%) of diagnoses**	**Age**	**Age & parental SES**	**Age & BMI**	**Age & diabetes**	**Age & diastolic blood**	**Age & IQ**	**All covariables except education & own SES**	**All covariables including education & own SES†**
Other non-affective psychoses/ schizophrenia/ bipolar disorder	12,595 (1.14)	1.91 (1.70, 2.15)	1.88 (1.67, 2.11)	1.32 (1.17, 1.49)	1.78 (1.58, 2.01)	1.85 (1.64, 2.08)	1.77 (1.57, 1.99)	1.16 (1.03, 1.31)	1.16 (1.02, 1.31)
Depressive disorders	9,402 (0.85)	1.30 (1.05, 1.60)	1.28 (1.04, 1.58)	1.29 (1.05, 1.60)	1.28 (1.03, 1.58)	1.28 (1.04 1.59)	1.24 (1.01, 1.54)	1.21 (0.98, 1.50)	1.22 (0.98, 1.53)
Neurotic/ adjustment disorders	48,039 (4.34)	1.52 (1.43, 1.62)	1.50 (1.41, 1.60)	1.44 (1.35, 1.53)	1.50 (1.41, 1.60)	1.50 (1.41, 1.59)	1.38 (1.30, 1.47)	1.29 (1.21, 1.37)	1.26 (1.18, 1.34)
Personality disorders	9,185 (0.83)	1.46 (1.31, 1.62)	1.41 (1.27, 1.56)	1.49 (1.34, 1.65)	1.46 (1.31, 1.62)	1.46 (1.30, 1.61)	1.26 (1.13, 1.40)	1.29 (1.16, 1.43)	1.24 (1.12, 1.38)
Alcohol-related disorders	2,688 (0.24)	1.92 (1.60, 2.31)	1.81 (1.50, 2.17)	1.83 (1.52, 2.20)	1.92 (1.60, 2.30)	1.89 (1.57, 2.27)	1.56 (1.30, 1.88)	1.46 (1.22, 1.76)	1.37 (1.12, 1.64)
Other substance use disorders	9,547 (0.86)	1.35 (1.12, 1.63)	1.32 (1.09, 1.59)	1.41 (1.17, 1.70)	1.34 (1.11, 1.62)	1.35 (1.12, 1.63)	1.21 (1.00, 1.46)	1.25 (1.04, 1.51)	1.22 (1.01, 1.48)

Abbreviations: BMI, body mass index; SES, socioeconomic status; IQ, intelligence quotient. *All adjustments include conscription testing centre and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. †Analyses based on subset aged ≥25 years at SES data collection in 1990 (n=666,190).

Supplemental table 3. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders at conscription (n=1,090,073, excluding men diagnosed with comorbid mental disorders at that time)

		Hazard ratio (95% CI)		
Diagnostic category	**No (%) of diagnoses**	**Adjusted for age**	**Adjusted for all covariables, except own SES & education†**	**Adjusted for all covariables, including own SES & education‡**
Other non-affective psychoses/schizophrenia/ bipolar disorder	109 (<0.001)	1.25 (0.40, 3.88)	1.03 (0.33, 3.18)	1.01 (0.33, 3.15)
Depressive disorders	1,741 (0.16)	1.27 (1.01, 1.63)	1.26 (0.99, 1.61)	1.24 (0.97, 1.59)
Neurotic/ adjustment disorders	31,848 (2.92)	1.41 (1.32, 1.52)	1.32 (1.23, 1.42)	1.29 (1.20, 1.39)
Personality disorders	7,453 (0.68)	1.43 (1.27, 1.61)	1.27 (1.13, 1.44)	1.22 (1.09, 1.39)
Alcohol-related disorders	1,609 (0.15)	1.74 (1.35, 2.24)	1.31 (1.01, 1.69)	1.23 (0.95, 1.59)
Other substance use disorders	2,657 (0.24)	1.38 (1.09, 1.75)	1.34 (1.05, 1.70)	1.27 (1.00, 1.62)

*All adjustments include conscription testing centre and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. †Further adjusted for parental SES, BMI, diastolic blood pressure, diabetes, intelligence. ‡Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=657,019).

Supplemental table 4. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders at conscription (n=1,090,073, excluding men diagnosed with a mental disorder at conscription and subsequently admitted to hospital with a mental disorder)

		Hazard ratio (95% CI)		
Diagnostic category	**No (%) of diagnoses**	**Adjusted for age**	**Adjusted for all covariables, except own SES & education†**	**Adjusted for all covariables, including own SES & education‡**
Other non-affective psychoses/schizophrenia/ bipolar disorder	11,388 (1.04)	1.74 (1.52, 1.99)	1.06 (0.92, 1.21)	1.05 (0.91, 1.21)
Depressive disorders	8,405 (0.77)	1.10 (0.85, 1.42)	1.04 (0.80, 1.33)	1.05 (0.80, 1.38)
Neurotic/ adjustment disorders	41,419 (3.78)	1.34 (1.25, 1.44)	1.14 (1.06, 1.22)	1.11 (1.04, 1.20)
Personality disorders	7,161 (0.65)	1.27 (1.12, 1.44)	1.14 (1.04, 1.29)	1.11 (0.98, 1.26)
Alcohol-related disorders	1,888 (0.17)	1.53 (1.20, 1.96)	1.18 (0.94, 1.50)	1.10 (0.86, 1.40)
Other substance use disorders	7,702 (0.70)	1.12 (0.87, 1.44)	1.06 (0.82, 1.36)	1.03 (0.79, 1.34)

*All adjustments include conscription testing centre and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. †Further adjusted for parental SES, BMI, diastolic blood pressure, diabetes, intelligence. ‡Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=657,637).

Supplemental table 5. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders at conscription (n=1,099,304, excluding men admitted to psychiatric hospital before conscription)

		Hazard ratio (95% CI)		
Diagnostic category	**No (%) of diagnoses**	**Adjusted for age**	**Adjusted for all covariables, except own SES & education†**	**Adjusted for all covariables, including own SES & education‡**
Other non-affective psychoses/schizophrenia/ bipolar disorder	12,342 (1.12)	1.93 (1.71, 2.17)	1.17 (1.04, 1.32)	1.16 (1.03, 1.32)
Depressive disorders	9,146 (0.83)	1.29 (1.04, 1.60)	1.21 (0.98, 1.50)	1.22 (0.98, 1.54)
Neurotic/ adjustment disorders	46,999 (4.28)	1.52 (1.43, 1.62)	1.28 (1.21, 1.37)	1.26 (1.18, 1.54)
Personality disorders	8,988 (0.24)	1.45 (1.31, 1.62)	1.28 (1.15, 1.43)	1.24 (1.11, 1.38)
Alcohol-related disorders	2,587 (0.24)	1.92 (1.59, 2.31)	1.46 (1.21, 1.76)	1.36 (1.13, 1.65)
Other substance use disorders	9,186 (0.84)	1.32 (1.09, 1.60)	1.23 (1.02, 1.50)	1.20 (0.98, 1.47)

*All adjustments include conscription testing centre and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. †Further adjusted for parental SES, BMI, diastolic blood pressure, diabetes, intelligence. ‡Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=662,983).

Supplemental table 6. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders on hospital admission after conscription, separately and fully adjusted for the covariables (n=1,099,304)

		Hazard ratios(95% confidence intervals							
		Adjustments							
Diagnostic category	**No (%) of diagnoses**	**Age**	**Age & parental SES**	**Age & BMI**	**Age & diabetes**	**Age & diastolic blood pressure**	**Age & IQ**	**All covariables except education & own SES**	**All covariables including education & own SES†**
Schizophrenia	5,961 (0.54)	1.49 (1.24, 1.80)	1.49 (1.24, 1.80)	1.59 (1.32, 1.91)	1.49 (1.24, 1.79)	1.46 (1.21, 1.75)	1.29 (1.07, 1.505)	1.37 (1.13, 1.64)	1.23 (1.02, 1.49)
Other non-affective psychoses	6,446 (0.59)	1.82 (1.52, 2.18)	1.82 (1.52, 2.19)	1.87 (1.56, 2.24)	1.83 (1.53, 2.19)	1.79 (1.15, 2.15)	1.61 (1.35, 1.93)	1.67 (1.39, 2.00)	1.58 (1.31, 1.90)
Bipolar disorders	2,566 (0.23)	1.62 (1.21, 2.18)	1.64 (1.22, 2.21)	1.63 (1.22, 2.20)	1.63 (1.21, 2.19)	1.61 (1.20, 2.17)	1.53 (1.14, 2.06)	1.56 (1.16, 2.10)	1.49 (1.09, 2.02)
Depressive disorders	14,519 (1.32)	2.09 (1.87, 2.33)	2.05 (1.84, 2.29)	2.15 (1.93, 2.40)	2.08 (1.86, 2.32)	2.14 (1.92, 2.40)	1.90 (1.70, 2.12)	1.94 (1.73 (2.16)	1.87 (1.68, 2.10)
Neurotic/ adjustment disorders	18,330 (1.67)	2.45 (2.24, 2.69)	2.3 (2.19, 2.62)	2.53 (2.31, 2.76)	2.45 (2.24, 2.68)	2.44 (2.23, 2.67)	2.19 (2.00, 2.40)	2.25 (2.05, 2.47)	2.17 (1.98, 2.38)
Personality disorders	6,917 (0.63)	2.01 (1.73, 2.33)	1.95 (1.68, 2.27)	2.11 (1.82, 2.45)	2.00 (1.72, 2.32)	1.99 (1.72, 2.31	1.71 (1.48, 1.99)	1.79 (1.54, 2.08)	1.63 (1.40, 1.91)
Alcohol-related disorders	28,391 (2.58)	2.62 (2.44, 2.81)	2.52 (2.35, 2.70)	2.68 (2.50, 2.87)	2.62 (2.44, 2.81)	2.60 (2.42, 2.78)	2.27 (2.12, 2.44)	2.31 (2.16, 2.48)	2.16 (2.01, 2.32)
Other substance use disorders	13,226 (1.20)	2.82 (2.53, 3.13)	2.76 (2.48, 3.07)	2.91 (2.62 3.24)	2.82 (2.53, 3.13)	2.81 (2.52, 3.12)	2.46 (2.21, 2.73)	2.54 (2.29, 2.83)	2.30 (2.06, 2.57)

Abbreviations: BMI, body mass index; SES, socioeconomic status; IQ, intelligence quotient. *All adjustments include conscription testing centre and year of examination. The reference group consists of men who were not diagnosed with the disorder in question. †Analyses based on subset aged ≥25 years at SES data collection in 1990 (n=662,983).

Supplemental table 7. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders on hospital admission after conscription, (n=1,076,588 excluding men diagnosed with comorbid mental disorders)

		Hazard ratios (95% confidence intervals)		
Diagnostic category	**No (%) of diagnoses**	**Adjusted for age**	**Adjusted for all covariables except education & own SES†**	**Adjusted for all covariables including education & own SES‡**
Schizophrenia	1,742 (0.16)	1.34 (0.94, 1.91)	1.23 (0.86, 1.75)	1.16 (0.81, 1.66)
Other non-affective psychoses	1,663 (0.15)	1.60 (1.05, 2.43)	1.49 (0.99, 2.26)	1.54 (1.01, 2.33)
Bipolar disorders	675 (0.06)	1.18 (0.59, 2.36)	1.18 (0.59, 2.36)	1.25 (0.63 (2.50)
Depressive disorders	5,441 (0.51)	1.61 (1.30, 1.99)	1.51 (1.22, 1.87)	1.52 (1.22, 1.88)
Neurotic/ adjustment disorders	8.005 (0.74)	2.25 (1.95, 2.61)	2.11 (1.82, 2.44)	2.08 (1.80, 2.41)
Personality disorders	905 (0.08)	1.20 (0.68, 2.12)	1.06 (0.60, 1.87)	0.99 (0.54, 1.77)
Alcohol-related disorders	14,925 (1.39)	2.33 (2.11, 2.58)	2.04 (1.84, 2.26)	1.96 (1.77, 2.18)
Other substance use disorders	4,236 (0.39)	2.67 (2.14, 3.33)	2.48 (1.99, 3.09)	2.23 (1.77, 2.80)

*All adjustments include conscription testing centre and year of examination. †Further adjusted for parental SES, and BMI, diagnosed diabetes, diastolic blood pressure, & intelligence, all measured at conscription. ‡Further adjusted for education and own SES in subset aged ≥25 years at SES data collection (n=645,117).

Supplemental table 8. Hazard ratios* (95% confidence intervals) for coronary heart disease events according to diagnosis of mental disorders at conscription or on subsequent hospital admission according to birth year†

		Hazard ratios (95% confidence intervals)		
Timing of diagnosis and year of birth	**No (%) of diagnoses**	**Adjusted for age**	**Adjusted for all covariables except education & own SES‡**	**Adjusted for all covariables including education & own SES§**
Conscription				
1951-1957 (n=328,857)	32,541 (9.90)	1.45 (1.37, 1.54)	1.28 (1.21, 1.36)	1.24 (1.17, 1.32)
1958-1965 (n=348,541)	15,361 (4.41)	1.95 (1.70, 2.33)	1.46 (1.27, 1.68)	1.40 (1.22, 1.61)
1966-1976 (n=430,126)	14,966 (3.48)	1.99 (1.36, 2.90)	1.33 (0.90, 1.96)	-
Hospital admission				
1951-1957 (n=328,112)	26,817 (8.17)	2.20 (2.07, 2.34)	2.01 (1.89, 2.14)	1.92 (1.81, 2.05)
1958-1965 (n=298,686)	16,831 (5.64)	2.86 (2.53, 3.22)	2.62 (2.32, 2.96)	2.53 (2.24, 2.87)
1966-1976 (n=425,242)	13,534 (3.18)	3.31 (2.31, 4.75)	2.72 (1.89, 3.93)	-

*All adjustments include conscription testing centre and year of examination. †Birth year groups are not evenly divided because of small number of CHD events in the later born men. Number of CHD events in men born 1951-57, 1958-1965 and 1966-1976 were 9397, 2541, and 440 respectively for the analyses of mental disorders at conscription and 9353, 1886 and 432 respectively for the analyses of mental disorders on hospital admission. ‡Further adjusted for parental SES, and BMI, diagnosed diabetes, diastolic blood pressure, & intelligence, all measured at conscription. §Further adjusted for education and own SES in subset aged ≥25 years at SES data collection, ie born before 1966).